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## Effect of Various Inspired Oxygen Concentrations on Pulmonary and Systemic Hemodynamics and Oxygenation during Resuscitation in a Transitioning Preterm Model

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### Abstract

**Background**—The Neonatal Resuscitation Program recommends initial resuscitation of preterm infants with low oxygen (O<sub>2</sub>) followed by titration to target preductal saturations (SpO<sub>2</sub>). We studied the effect of resuscitation with titrated O<sub>2</sub> on gas exchange, pulmonary and systemic hemodynamics.

**Methodology**—Twenty-nine preterm lambs (127d-gestation) were randomized to resuscitation with 21%O<sub>2</sub> (n=7), 100%O<sub>2</sub> (n=6) or initiation at 21% and titrated to target SpO<sub>2</sub> (n=16). Seven healthy term control lambs were ventilated with 21%O<sub>2</sub>.

**Results**—Preductal SpO<sub>2</sub> achieved by titrating O<sub>2</sub> was within the desired range similar to term lambs in 21%O<sub>2</sub>. Resuscitation of preterm lambs with 21 and 100%O<sub>2</sub> resulted in SpO<sub>2</sub> below and above the target respectively. Ventilation of preterm lambs with 100%O<sub>2</sub> and term lambs with 21%O<sub>2</sub> effectively decreased pulmonary vascular resistance (PVR). In contrast, preterm lambs with 21%O<sub>2</sub> and titrated O<sub>2</sub> demonstrated significantly higher PVR than term lambs on 21%O<sub>2</sub>.

**Conclusion(s)**—Initial resuscitation with 21%O<sub>2</sub> followed by titration of O<sub>2</sub> led to suboptimal pulmonary vascular transition at birth in preterm lambs. Ventilation with 100%O<sub>2</sub> in preterm lambs caused hyperoxia but reduced PVR similar to term lambs on 21%O<sub>2</sub>. Studies evaluating initiation of resuscitation at higher O<sub>2</sub> concentration followed by titration based on SpO<sub>2</sub> in preterm neonates are needed.

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## Introduction

The optimal concentration of supplemental oxygen during initial resuscitation of premature infants remains controversial. The International Liaison Committee on Resuscitation (ILCOR) recommends initiating resuscitation of preterm newborns (less than 35 weeks postmenstrual age-PMA) with a low inspired oxygen concentration (30%) (strong recommendation, moderate-quality evidence) (1). ILCOR does not recommend the use of high concentration (65%) of supplemental oxygen (1, 2). Similarly, the Neonatal Resuscitation Program (NRP) recommends that resuscitation of preterm newborns < 35 weeks gestation at birth should be initiated with low concentration of inspired oxygen (30%), and the oxygen concentration should be titrated to achieve preductal SpO<sub>2</sub> targets (3). The evidence for this recommendation comes from analysis of 7 randomized control trials (RCTs) (4–10) which have shown no advantage of using high oxygen compared to low oxygen for the critical outcome of mortality (Relative risk (RR) 1.48; 95% confidence interval (CI) 0.8 – 2.73). After these recommendations were published, a large RCT by Oei et al. targeting SpO<sub>2</sub> between 65–95% up to 5 min of postnatal life and 85–95% from 5 min until NICU admission has shown that the mortality was high in infants <28 weeks PMA initially resuscitated with 21% O<sub>2</sub> compared to 100% O<sub>2</sub> (RR 3.9 (1.1–13.4); P= 0.01 – non-prespecified analysis) (11). A retrospective study by Rabi et al. comparing infants 27 weeks' gestation before and after 2006, when the policy regarding initial oxygen concentration for preterm infants in the delivery room was changed from 100% to <100% oxygen and titration to achieve target SpO<sub>2</sub> was published in 2015 (12). This Canadian Neonatal Network study has shown that the adjusted odds ratio (AOR) for the primary outcome of severe neurologic injury or death was higher in the lower oxygen group (AOR 1.36; 95% CI 1.11–1.66) and in those resuscitated with 21% oxygen (AOR 1.33; 95% CI 1.04–1.69), when compared to 100% oxygen. Despite the current evidence, the optimal concentration of supplemental oxygen for initial resuscitation of preterm neonates remains unclear.

The effect of titrating inspired oxygen during resuscitation of a newly born preterm model on gas exchange and hemodynamics is not known. Our objectives were to determine the effect of resuscitating a preterm lamb model with 21% O<sub>2</sub>, 100% O<sub>2</sub> and titrating supplemental oxygen as per NRP recommended preductal saturations on i) oxygen saturations, ii) arterial oxygenation and iii) systemic and pulmonary hemodynamics.

## Methodology

This study was approved by the Institutional Animal Care and Use Committee (IACUC) of University at Buffalo. Time-dated pregnant ewes (May Farms, Buffalo Mills, PA) at 127–128d gestation (preterm equivalent, the term equivalent 147 – 150d) were sedated, intubated and ventilated with 21–30% oxygen and anesthetized with 2% isoflurane. Before delivery, the lambs were randomized using sequential opaque envelopes (target randomization ratio- 1:1:3 – 21% O<sub>2</sub>, 100% O<sub>2</sub> and titrated O<sub>2</sub> respectively – see below). Preterm lambs were partially exteriorized via a cesarean section. They were instrumented as described below while on placental circulation and maternal anesthesia. The ewes did not receive prenatal steroids. Term lambs at 142d gestation (to reduce the risk of spontaneous labor) were used

as controls. The instrumentation of these lambs were as described previously {Rawat, 2016 #39}.

**Monitoring –** Preductal saturations were measured by Masimo radical pulse oximeter probe (Masimo, Irvine, CA) which was placed on the right forelimb. We targeted preductal saturations based on current NRP recommendations (3). A respiratory monitor (NM3 Philips, Respironics, MA) with a mainstream end-tidal carbon dioxide detector (ETCO<sub>2</sub>) was attached to the tracheal tube (13, 14). Cerebral saturation was measured by NONIN (SenSmart Model X-100, Plymouth, MN) regional oximetry. The cerebral regional saturations (CrSO<sub>2</sub>) were measured in preterm lambs but not in term lambs (controls). The carotid arterial oxygen content was measured as described previously in preterm lambs (15). The oxygen extraction was calculated in preterm lambs as a product of left carotid blood flow and the difference in arterial oxygen content (carotid artery) and the venous oxygen content (jugular bulb) (15). Venous gases were not available in term lambs.

**Randomization and protocol –** After instrumentation and surfactant instillation (Infasurf 3ml/kg, ONY), the lamb was delivered following early cord clamping. Based on the randomization arm, preterm lambs were resuscitated with 21% O<sub>2</sub> (group 1) or 100% O<sub>2</sub> (group 2) regardless of preductal SpO<sub>2</sub>. In the targeted oxygen group (group 3), the O<sub>2</sub> was initiated at 21% and titrated to maintain oxygen in the NRP specified range as mentioned above. If preductal SpO<sub>2</sub> was outside this range, inspired oxygen was adjusted by 5% every 15 s. Term healthy lambs were ventilated with 21% irrespective of SpO<sub>2</sub> and served as controls (16). After the first 30 min, the variable O<sub>2</sub> group was further subdivided into three saturation target ranges to mimic NeOPrOM studies (85–89%, 90–94% and 95–99% - data not shown in this manuscript) (17). As “positive” and “negative” controls, we ventilated two group of lambs continuously with 21% oxygen and 100% oxygen irrespective of SpO<sub>2</sub>. Our original intention was to study 6 lambs in each group. In the titrated group we intended to study 18 lambs, but 2 were lost during instrumentation. Because of this reason, the variable group has approximately 3 times the number of lambs in the 21% and 100% categories.

Ventilation was initiated with the Siemens Servo 300A (Maquet Medical, Salt Lake City, Utah) with a peak inspiratory pressure (PIP) of 30–35 cm H<sub>2</sub>O and a PEEP of 5–6 cm H<sub>2</sub>O to target a tidal volume of 8–9 ml/kg in preterm lambs. Tidal volume data were not available in the term lambs. Arterial blood gases were drawn at birth, 1, 2 and 5 min after birth followed by every 5 min for the first 30 min. Systemic and pulmonary hemodynamics were continuously recorded using AcqKnowledge Acquisition and Analysis Software (BIOPAC Systems, Goleta, CA). Sample size and power calculation - Based on previous studies, to detect a difference in pulmonary vascular resistance of 0.15 mmHg/ml/kg/min we needed 6 lambs in each group (18, 19). A power estimate was performed by one-way ANOVA, using statistical analysis software 9.4 (SAS, NC). With the current randomization, the power to detect the difference in PVR is 0.85 with an alpha of 0.05.

**Statistics –** Categorical variables are presented as numbers and percentages while continuous variables as means and standard deviations. Data were analyzed using chi-square, t-test and ANOVA. Statistical significance was set at less than 5%.

## Results

Baseline characteristics of lambs before resuscitation are shown in Table 1. There were a total of 36 lambs in the study: six preterm lambs ventilated with 100% O<sub>2</sub>, seven preterm lambs with 21% O<sub>2</sub>, sixteen preterm lambs ventilated targeting SpO<sub>2</sub> range and seven term lambs ventilated with 21% O<sub>2</sub>. The weight of the term lambs was significantly higher compared to preterm lambs (table 1).

**Saturation:** In the first 30 minutes after birth, use of 21% and 100% O<sub>2</sub> resulted in SpO<sub>2</sub> below and above the NRP recommended target range respectively. Titrating oxygen in preterm lambs and use of 21% oxygen in term lambs resulted in NRP recommended target saturations (Figure 1a). Among preterm lambs, the time spent within the target SpO<sub>2</sub> as recommended by NRP was 10% in 100% O<sub>2</sub> group, 47% with the titrated O<sub>2</sub> group and 30% in 21% O<sub>2</sub> group. Term lambs ventilated with 21% O<sub>2</sub> spent 65% of the first 30 minutes within the NRP recommended target range (significantly higher than preterm lambs,  $p<0.001$ ).

**FiO<sub>2</sub>:** The inspired oxygen concentration required to maintain targeted saturations in the titrated FiO<sub>2</sub> preterm group is shown in Figure 1b (Median FiO<sub>2</sub> 0.31 (interquartile range: 0.21 – 0.40)).

**Tidal volume and arterial carbon dioxide (Figure S1):** There was no difference in tidal volumes in preterm lambs (Figure S1a). The term lambs had lower PaCO<sub>2</sub> compared to preterm lambs and these values were statistically different (Figure S1b) ( $p<0.01$ ).

**Alveolar Oxygenation (PAO<sub>2</sub>) (Figure 2):** The calculated PAO<sub>2</sub> with 100% O<sub>2</sub>, titrated O<sub>2</sub> and 21% O<sub>2</sub> were  $643\pm24.4$  mmHg,  $244\pm156$  mmHg and  $95\pm24.2$  mmHg and were significantly different ( $p<0.001$ ) (Figure 3). The PAO<sub>2</sub> in term lambs ( $99\pm11$  mmHg) resuscitated with 21% O<sub>2</sub> were similar to preterm 21% inspired oxygen group.

**Arterial oxygenation:** Arterial oxygen tension (PaO<sub>2</sub>) was highest with 100% O<sub>2</sub> ( $256\pm144$  mmHg) and was higher than 21% O<sub>2</sub> group of preterm lambs ( $39\pm16$  mmHg,  $p<0.001$ ), titrated oxygen group ( $60\pm36$  mmHg,  $p<0.001$ ) and in term controls ( $37\pm10$  mmHg,  $p<0.001$ ) in the first 30 minutes. The PaO<sub>2</sub> was higher in preterm lambs resuscitated with titrated O<sub>2</sub> group compared to preterm lambs resuscitated with 21% O<sub>2</sub> ( $p=0.039$ ) (Figure 3).

**Heart rate:** Heart rates were similar in preterm lambs resuscitated with 100% O<sub>2</sub> ( $183\pm27$ /min), 21% O<sub>2</sub> ( $175\pm27$ /min), titrated O<sub>2</sub> ( $173\pm37$ /min) and term controls ( $180\pm25$ /min).

**Pulmonary blood flow (PBF):** The PBF was highest in preterm lambs resuscitated with 100% O<sub>2</sub> and was different from preterm lambs resuscitated with 21% O<sub>2</sub> ( $p<0.001$ ), titrated oxygen ( $p<0.001$ ) but similar to term controls (Figure 4a).

**Carotid blood flow (CBF):** The CBF was similar in all four groups (Figure 4b).

**Cerebral regional saturation (CrSO<sub>2</sub>), carotid arterial oxygen content and oxygen extraction (Figure S2):** The CrSO<sub>2</sub> (figure S2a) and carotid arterial oxygen content (figure S2b) was

higher and statistically different in the lambs that received 100% O<sub>2</sub> (p<0.01). The oxygen extraction was not different among the preterm lambs (figure S2c).

Systemic mean blood pressures (SBP) and pulmonary arterial mean blood pressures (PAP) (Figure 5): Left to right ductal flow is an essential contributor of pulmonary blood flow immediately after birth (20). The pressure gradient driving net ductal flow is the difference between systemic and pulmonary blood pressures. Mean systemic blood pressure was significantly higher than the pulmonary mean blood pressure in term lambs ventilated with 21% O<sub>2</sub> (SBP: 80.2±14.4 mmHg, PBP: 48.4±7.2 mmHg, p<0.001), preterm lambs ventilated with 100% O<sub>2</sub> (SBP:57.8±10.5 mmHg, PBP:38.4±8.3 mmHg, p<0.001) and in preterm lambs where the inspired oxygen was titrated to maintain saturations (SBP: 49.4±8.2mmHg, PBP: 41.5±11.1 mmHg, p<0.01). In contrast, preterm lambs ventilated with 21% O<sub>2</sub> had similar systemic and pulmonary arterial pressures with no gradient across the ductus throughout the first 30 minutes of the postnatal period (SBP:49.1±9.0 mmHg, PBP:47.4±7.4 mmHg, p=0.25 as shown in Figure 5D). The difference in mean systemic blood pressure and pulmonary arterial pressure over the first 30 minutes after birth was significantly higher in term lambs ventilated with 21% oxygen and preterm lambs ventilated with 100% oxygen compared to preterm lambs ventilated with titrated O<sub>2</sub> and 21% oxygen.

Compared to fetal values, pulmonary arterial pressure significantly decreased over the first 30 minutes in term lambs (21% oxygen) and preterm lambs ventilated with 100% oxygen. There was no significant difference in pulmonary arterial pressure at 30 min after birth when compared to fetal values in preterm lambs ventilated with 21% oxygen. In lambs ventilated with titrated O<sub>2</sub>, the difference between fetal pulmonary arterial pressure compared to pressure at 30 min of postnatal age had a p-value of 0.05.

Pulmonary vascular resistance (PVR) (Figure 6): The PVR was highest in preterm lambs ventilated with 21% O<sub>2</sub> (1.5±0.9 mmHg/ml/kg/min) and was significantly different from preterm lambs ventilated with 100% O<sub>2</sub> (0.6±0.3 mmHg/ml/kg/min, p<0.001), titrated O<sub>2</sub> (0.9±0.6 mmHg/ml/kg/min, p<0.001) and term lambs ventilated with 21% O<sub>2</sub> (0.7±0.3 mmHg/ml/kg/min, p<0.001). The PVR was significantly higher in the titrated oxygen group compared to the 100% O<sub>2</sub> group in preterm lambs (p=0.03) Both these groups were not statistically different from term lambs resuscitated with 21% O<sub>2</sub>.

## Discussion

Effective ventilation of the lungs with optimal inspired O<sub>2</sub> is the key factor mediating pulmonary transition at birth leading to an 8 to 10-fold increase in PBF permitting effective gas exchange (21–23). In this study, we have demonstrated that ventilation with 21% O<sub>2</sub> in term lambs without lung pathology reduced pulmonary arterial pressure and increased PBF. Ventilation of preterm lambs with 100% O<sub>2</sub> significantly reduced pulmonary arterial pressure, established a significant pressure gradient across the ductus and marginally increased PBF, similar to that seen in term lambs ventilated with 21% O<sub>2</sub>. In contrast, ventilation with 21% O<sub>2</sub> in preterm lambs did not significantly reduce pulmonary arterial pressure over the first 30 minutes after birth and the increase in PBF was significantly lower than that in term lambs. Interestingly, initiation of ventilation at 21% O<sub>2</sub> and titration of

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FiO<sub>2</sub> targeting NRP recommended SpO<sub>2</sub> range led to a modest decrease in pulmonary arterial pressure, but the increase in PBF was significantly lower than that achieved in term lambs. To our knowledge, this is the first study evaluating gas exchange, systemic and pulmonary hemodynamics, and cerebral oxygen delivery in a transitioning preterm model targeting the NRP recommended SpO<sub>2</sub> ranges. These differences were achieved with similar tidal volumes and PaCO<sub>2</sub> values among the three groups of preterm lambs suggesting that these differences were mainly due to variation in oxygen tension (figure S1).

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The supplemental oxygen needed in a preterm neonate requiring assisted ventilation that facilitates the pulmonary vascular transition remains a subject of controversy. It is not known if the target saturation range recommended by NRP is adequate to increase pulmonary blood flow and establish lungs as the site of gas exchange in extremely preterm neonates requiring positive-pressure ventilation. We demonstrate that titrating inspired oxygen resulted in SpO<sub>2</sub> in the desired range and 100% inspired O<sub>2</sub> resulted in saturations above the target range. These results are different from the study in 287 preterm infants by Oei et al. (11). In their study, initiation of resuscitation with 21% oxygen and titration resulted in mean SpO<sub>2</sub> below the target range for the first 7–8 minutes after birth. We speculate that this difference was secondary to: (a) all lambs in our study being intubated (and having received surfactant), compared to only 30% of infants in the Oei et al. study; (b) SpO<sub>2</sub> values were available in the very first minute and O<sub>2</sub> was adjusted immediately after birth; (c) we titrated O<sub>2</sub> by 5% every 15 seconds as compared to 10% every minute in the clinical study; (d) our lambs were not exposed to antenatal steroids, while 97% of mothers in the Oei et al. study had received antenatal steroids and finally (e) species differences.

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Dawson et al. have published changes in preductal SpO<sub>2</sub> after birth for the term and preterm infants with no supplemental oxygen (24) (25). The supplemental oxygen required to achieve target SpO<sub>2</sub> was higher (30% – 67%) in extremely preterm infants less than 27 6/7 weeks compared to moderate preterm infants 28 – 32 weeks (23% – 43%). Similarly, Phillipos et al. have shown that infants <28 weeks gestation requiring PPV who were initially ventilated with 30% oxygen had markedly lower saturations compared to NRP targets (25). With decreasing gestational age, higher FiO<sub>2</sub> is necessary to achieve target oxygen saturations (25). We found similar differences between term lambs where target SpO<sub>2</sub> could be achieved by ventilation with 21% O<sub>2</sub> but required 44 ± 4% oxygen to achieve the same target in preterm lambs (equivalent gestational age <28 weeks in humans). Interestingly, the preductal PaO<sub>2</sub> achieved by preterm lambs ventilated with 21% O<sub>2</sub> was similar to that in term lambs. We do not have a physiologic explanation for the difference in SpO<sub>2</sub> between preterm and term lambs ventilated with 21% oxygen, although for a given SpO<sub>2</sub> value there may be a wide range of PaO<sub>2</sub> values (26). In an individual patient analysis by Oei et al. which included 706 infants, only 11% reached NRP recommended SpO<sub>2</sub> of 80–85% by 5 minutes (27). Infants who did not reach 80% SpO<sub>2</sub> by 5 minutes had 2.4 times higher mortality and 4.5 times more likely to develop severe intraventricular hemorrhage (27) (28). The data from this study need to be interpreted with caution as it is unclear if the infants were sick and could not achieve > 80% SpO<sub>2</sub> in spite of receiving high FiO<sub>2</sub> or if less supplemental oxygen was provided resulting in SpO<sub>2</sub> < 80%. Furthermore, a study by Follett et al. concluded that ‘there was a lag time of approximately 30 s to achieve the FiO<sub>2</sub> at the facemask’. Slower change in oxygen could have yielded different results. Our study was



different from the clinical situation where intubation and surfactant delivery was performed before delivery.

Ventilation with 100% O<sub>2</sub> resulted in supra-physiological PaO<sub>2</sub> (Figure 3). The PaO<sub>2</sub> in the titrated oxygen group was significantly higher than preterm lambs resuscitated with 21%. Interestingly, delivery of more oxygen to the brain did not result in higher oxygen extraction (figure S2) but resulted in higher CrsO<sub>2</sub>. Previous studies have shown that resuscitation with higher oxygen can lead to oxidative stress injury, inflammation and chronic lung disease (9, 29). Kapadia et al. have shown that when resuscitation was initiated with low oxygen and titrated to target NRP recommended SpO<sub>2</sub>, the infants had low cumulative oxygen exposure, lower oxidative stress and decreased respiratory morbidities (5). Continuous use of 100% O<sub>2</sub> may lead to hyperoxic injury and may cause the arrest of lung development (30–32). In an asphyxiated term lamb model, we have shown that use of 100% oxygen increases oxidative stress (33). Previously, we have also shown that oxidized glutathione activity correlated with PaO<sub>2</sub> in a preterm lamb model (34). In a prospective clinical study by Castillo et al. maintaining saturations between 85 – 93% resulted in PaO<sub>2</sub> levels of 40 to 80 mmHg, 87% of the time in neonate (35). In our study, titrating oxygen to maintain SpO<sub>2</sub> in target range resulted in an average PaO<sub>2</sub> of 54 mmHg while the continuous use of 21% resulted in an average PaO<sub>2</sub> of 35 mmHg during the first 30 minutes after birth. A PaO<sub>2</sub> of at least 45 mmHg is required for successful pulmonary vascular transition (16, 19, 33, 36). To achieve a delicate balance between hyperoxia and hypoxia, maintaining SpO<sub>2</sub> in the target range suggested by NRP may be safe until more evidence is available in preterm infants.

At birth with the establishment of respiration, pulmonary vascular resistance (PVR) decreases, PBF increases and ductal shunt from right-to-left changes to left-to-right (37, 38). Heart rate is the single most important predictor of adequate ventilation (3). Since our lambs were intubated and ventilated immediately after birth, we did not find any difference in heart rate between the groups. In contrast, Oei et al. demonstrated a lower heart rate in preterm infants resuscitated initially with 21% O<sub>2</sub> when compared to 100% O<sub>2</sub> (11). We observed higher PBF in preterm lambs ventilated with 100% O<sub>2</sub> similar to that seen in term lambs ventilated with 21% oxygen. Although PAO<sub>2</sub> and PaO<sub>2</sub> achieved by ventilation with 21% oxygen were similar in preterm and term lambs, the increase in pulmonary blood flow was significantly lower in preterm lambs. We speculate that this difference might be secondary to lung disease, ventilation-perfusion mismatch, the lower sensitivity of pulmonary vasculature to oxygen and/or due to differences in pressure gradient across the ductus.

The difference in systemic and pulmonary blood pressures were strikingly different in preterm lambs ventilated with different oxygen concentrations (Figure 5). The gradient across the ductus (difference in systemic and pulmonary pressures) in term lambs ventilated with 21% was higher than preterm lambs ventilated with 21% O<sub>2</sub> or titrated FiO<sub>2</sub> and similar to preterm lambs ventilated with 100% O<sub>2</sub>. The difference in pulmonary and systemic pressures reached a statistically significant difference in the titrated oxygen group but not in 21% preterm lambs.

Why is the pressure gradient across the ductus important in the golden hour of resuscitation especially in preterm infants? Once the cord is clamped, systemic blood pressure increases



and with ventilation, there is a significant decrease in PVR. The increase in right ventricular output is not the sole contributor to increased blood flow to the lung after birth (38, 39). The change in shunt in the ductus which switches to left-to-right contributes to right ventricular output immediately after birth. This transition is a critical process that helps sustain and stabilize PBF, pulmonary venous return and thus maintaining left ventricular output (20, 37, 39). Our study highlights the effect of using various oxygen concentration in this critical process.

The drop in PVR was highest with the use of 100% O<sub>2</sub> in preterm lambs and was similar to 21% oxygen use in term lambs. Use of 21% O<sub>2</sub> in preterm lambs resulted in no change in PVR by 30 minutes of postnatal age compared to fetal values. Titrating oxygen to maintain target SpO<sub>2</sub> lead to a drop in PVR by 57% at 30 minutes of life compared to the fetal PVR. The decrease in PVR, in this case, can be directly related to the PaO<sub>2</sub> achieved by various oxygen concentration during resuscitation. We have previously shown in an asphyxiated model with lung disease, use of 21% O<sub>2</sub> may not be adequate to achieve pulmonary vasodilation secondary to low PaO<sub>2</sub> levels (16), although in a term model without lung disease use of 21% O<sub>2</sub> did result in significant decrease in PVR (16, 19).

The suboptimal increase in PBF with the initiation of ventilation with 21% oxygen and titration to achieve target SpO<sub>2</sub> (when compared to 100% O<sub>2</sub> ventilation) is a concern. The recent evidence from Oei et al. study shows that extremely preterm infants (< 28 weeks' gestation) had higher mortality when ventilation was initiated with 21% O<sub>2</sub> as compared to 100% O<sub>2</sub> further emphasizing the importance of this finding (11). In the same study, the most common cause of death in preterm infants resuscitated initially with 21% O<sub>2</sub> was respiratory failure (which may potentially be secondary to RDS complicated by impaired pulmonary vascular transition). It is important to recognize that the results in < 28 weeks' gestation preterm infants in this study were not part of a prespecified analysis and that the sample size was small. However, increased mortality with lower oxygen supplementation is a concern. These findings are similar to the retrospective Canadian study which showed higher mortality and evidence of higher neurologic injury in preterm infants resuscitated with < 100% oxygen (12). We speculate that inadequate pulmonary vascular transition in preterm infants resuscitated with lower FiO<sub>2</sub> may potentially play a role in mediating higher respiratory morbidity.

Studies in postnatal preterm infants have shown that 100% O<sub>2</sub> inhalation results in ~15% reduction in cerebral blood flow (40, 41). Exposure to oxygen at birth results in prolonged cerebral vasoconstriction in preterm infants (6). However, a recent study in stable preterm infants did not demonstrate cerebral vasoconstriction following hyperoxia (42). The relationship between hyperoxia and cerebral blood flow are complex and are elegantly summarized in a recent editorial (43).

Cerebral vasoconstriction following 100% oxygen may potentially protect the brain from hyperoxic injury. However, in our study, we found no reduction in CBF in spite of 100% oxygen resuscitation in preterm lambs. The cerebral saturations and the carotid arterial oxygen content were highest with 100% O<sub>2</sub> resuscitation resulting in increased delivery of oxygen, but oxygen extraction was similar between the 3 groups of preterm lambs.

Premature neonates are at risk of hyperoxic brain injury, especially when exposed to supraphysiological oxygen levels compared to their fetal environment. Gerstner et al. have shown that hyperoxia could lead to maturation-dependent cell death in the developing white matter (44). The lack of reduction in cerebral blood flow despite high PaO<sub>2</sub> levels suggests that the risk of cerebral hyperoxia is considerably higher in preterm infants initially resuscitated with 100% oxygen and may contribute to brain injury. We acknowledge that species differences and similar PaCO<sub>2</sub> levels between groups in our study may account for some of the variations among studies. Based on these findings, resuscitators should exercise caution and avoid initiating resuscitation with 100% oxygen in preterm infants and support the currently planned study comparing 60% and 30% oxygen for initial resuscitation of preterm infants ((PRESOX) (NCT01773746)).

There are several limitations to this study. Ventilating these lambs with an endotracheal tube and prophylactic surfactant helped achieved targeted saturations early and would have been different if bag and mask ventilation was initiated. The time spent in the prespecified saturation range in the titrated O<sub>2</sub> group was only 47%, while 30% were above and the remainder of the 23% were below the range. We found it practically difficult to maintain saturations in 5% range in the first 5 minutes. During the 5 – 30 min period, the target range broadens to 85–95% and targets were achievable. Improved time spent within the SpO<sub>2</sub> range may have altered the pulmonary hemodynamics in these lambs. We performed immediate cord clamping in our study and did not evaluate the effect of placental transfusion during initial ventilation (3, 45, 46). The ductal flow in this study was not measured/analyzed. None of these lambs had bradycardia and did not require chest compressions or epinephrine (47, 48). All these experiments were done in a controlled setting with personnel available to titrate oxygen every 15 seconds which may be different in a real-life scenario in a busy delivery room (49). We did not study initiation of ventilation with 65–100% oxygen followed by decreasing FiO<sub>2</sub> based on SpO<sub>2</sub> – this may be an important arm that requires further study. We continued ventilating these infants for 6 hours and did not obtain tissues at the end of the 30 min period. Hence, oxidative stress markers are not available at the end of 30 minutes to evaluate the injury.

## Conclusion

Titration of oxygen starting from 21% O<sub>2</sub> successfully achieved target saturations. Continuous use of 100% and 21% oxygen resulted in saturations above and below the target range. Use of 100% oxygen resulted in better pulmonary transition as evidenced by the significant difference in systemic and pulmonary hemodynamics compared to 21% use in preterm lambs but was similar to term controls ventilated with 21% O<sub>2</sub>. Ventilation with 100% O<sub>2</sub> in preterm lambs caused hyperoxia and did not increase oxygen delivery to the brain but reduced PVR similar to term lambs on 21% O<sub>2</sub>. Initiation of resuscitation with low oxygen (21%) and titration based on NRP recommended target saturations, resulted in significantly lower increase in PBF compared to term lambs and may not be adequate. In the future, studies evaluating the effect of resuscitating preterm infants with higher initial oxygen concentration (60–100%) and titrating down targeting saturations are needed. We eagerly await additional studies such as the ‘Study of Room Air Versus 60% Oxygen for Resuscitation of Premature Infants (PRESOX) (NCT01773746)’ for more insight.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

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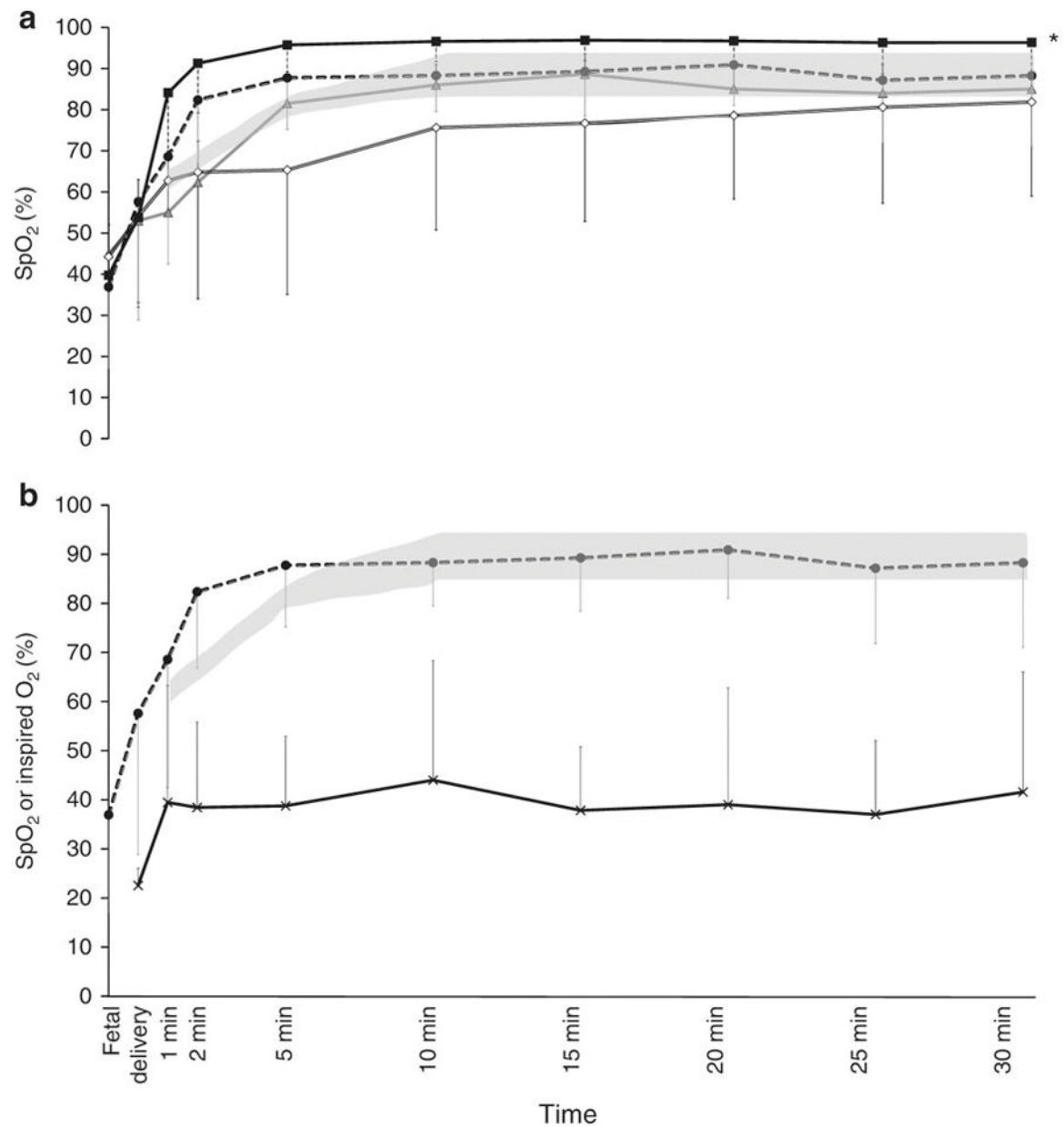
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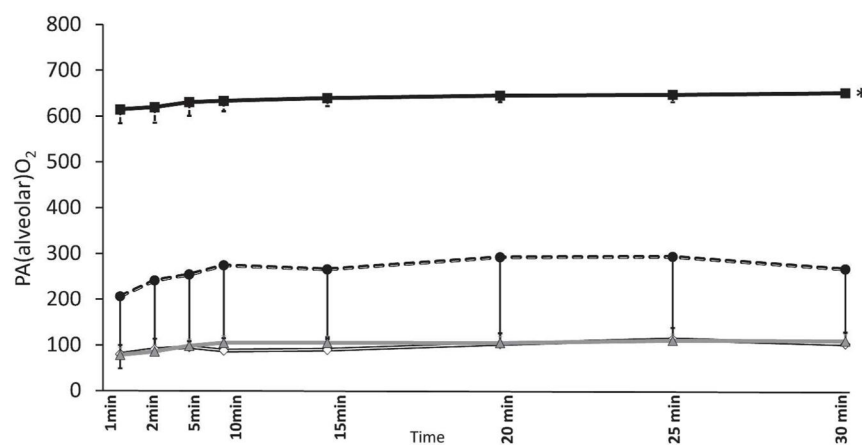


**Figure 1.**

a) Changes in saturations (SpO<sub>2</sub>) with 100% inspired oxygen preterm lambs (closed square), 21% oxygen preterm lambs (open diamond), titrated oxygen (closed circle) and term 21% oxygen controls (triangle). The shaded area shows the NRP recommended saturation targets

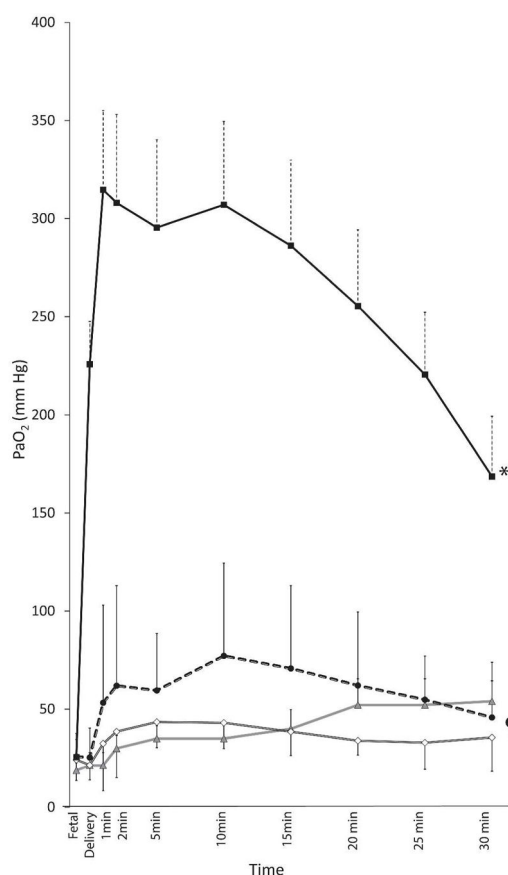
b) Changes in titrated oxygen (cross) and saturations (closed circle) in titrated oxygen group. Hyphenated lines/shaded area shows the NRP recommended saturation targets.





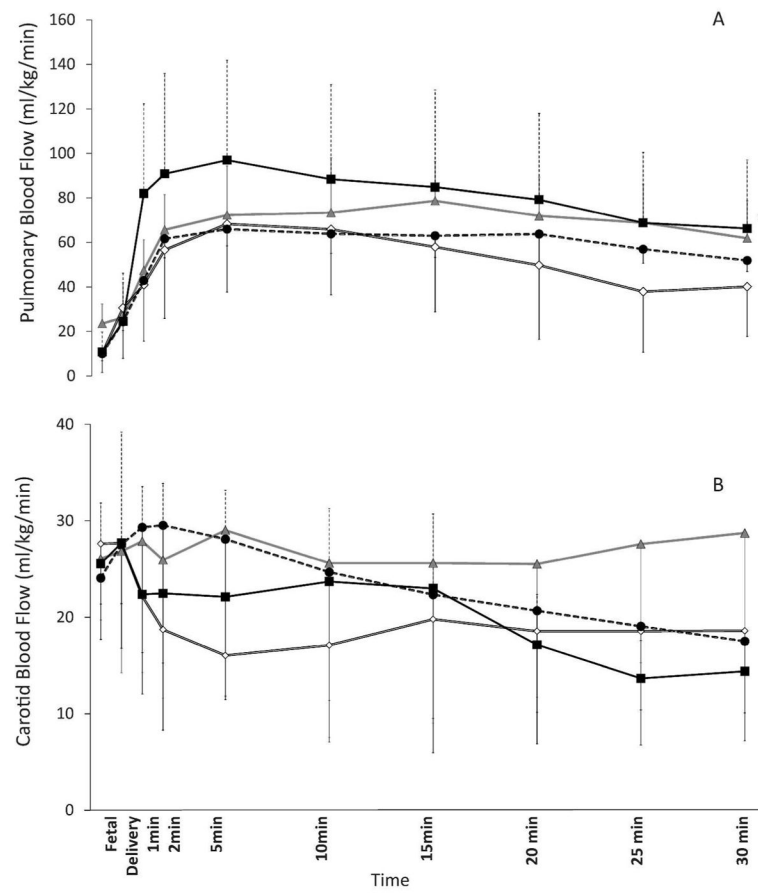
**Figure 2.**

PAO<sub>2</sub> (alveolar oxygenation) are shown in figure 3. 100% inspired oxygen preterm lambs (closed square), 21% oxygen preterm lambs (open diamond), titrated oxygen (closed circle) were different. \*p<0.001 by ANOVA. Use of 21% in the term (triangle) and preterm lambs showed similar PAO<sub>2</sub>.



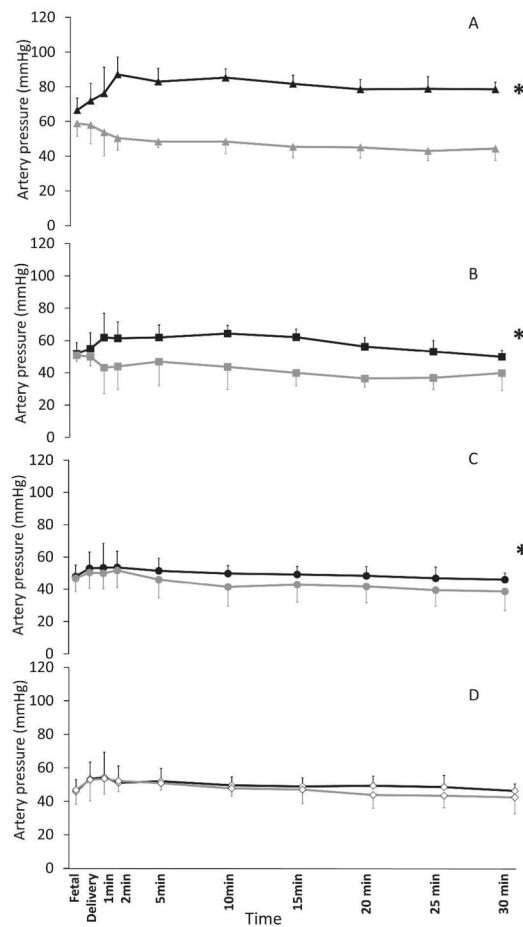
**Figure 3.**

Arterial Oxygen tension ( $\text{PaO}_2$ ) changes with 100% oxygen preterm lambs (closed square), 21% oxygen preterm lambs (open diamond), titrated oxygen (closed circle) and term 21% (triangle) oxygen controls (triangle). \* 100% preterm oxygen statistically different from the rest by ANOVA ( $p < 0.001$ ). ¶ Titrated oxygen group different from 21% preterm by ANOVA ( $p < 0.01$ ).

**Figure 4.**

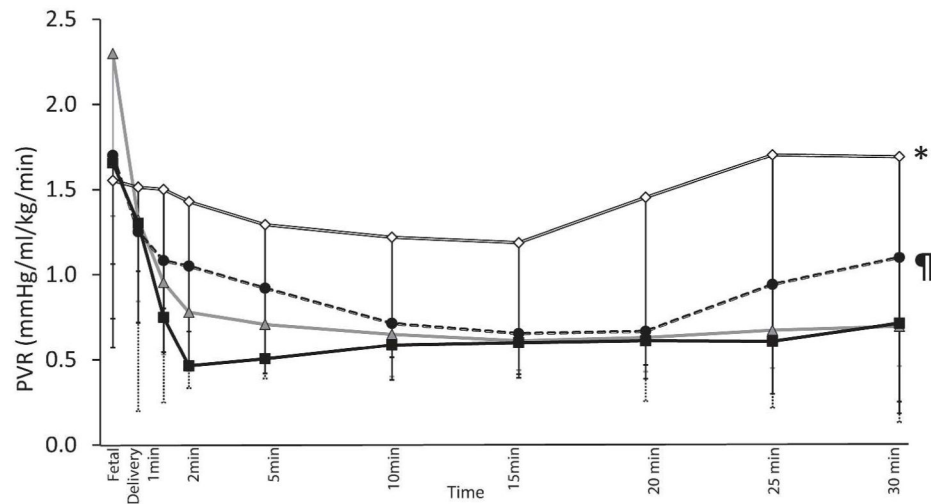
a) Left pulmonary arterial blood flow (PBF) changes with 100% oxygen preterm lambs (closed square), 21% oxygen preterm lambs (open diamond), titrated oxygen (closed circle) and term 21% controls (triangle). \*100% preterm lambs were different from preterm 21% and titrated O<sub>2</sub> group. But not different from term 21%  $p < 0.001$  by ANOVA.

b) Left carotid blood flow (CBF) changes with 100% oxygen preterm lambs (closed square), 21% oxygen preterm lambs (open diamond), titrated oxygen (closed circle) and term 21% controls (triangle). The flows were not different.



**Figure 5.**

Systemic and pulmonary arterial mean pressures in term 21% oxygen (A), preterm 100% oxygen (B), preterm titrated oxygen (C) and preterm 21% oxygen (D). A) Black and gray triangles represent the mean systemic and mean pulmonary arterial pressures in term lambs ventilated with 21% inspired oxygen (controls). B) Black and gray squares represent the mean systemic and mean pulmonary arterial pressures in preterm lambs resuscitated with 100% oxygen. C) Black and gray circles represent the mean systemic and mean pulmonary arterial pressures in preterm lambs resuscitated with oxygen titrated to achieve target SpO<sub>2</sub>. D) Open black and gray diamonds represent the mean systemic and mean pulmonary arterial pressures in preterm lambs resuscitated with 21% inspired oxygen concentration. \*  $p < 0.001$  by ANOVA – the difference between systemic and pulmonary pressures.



**Figure 6.**

Pulmonary vascular resistance (PVR) changes in preterm lambs resuscitated with 100% oxygen (closed squares), 21% oxygen (open diamonds), and titrated inspired oxygen to maintain target SpO<sub>2</sub> (closed circles). Term lambs ventilated with 21% inspired oxygen (controls - triangles) are shown by a hyphenated line. \* 21% preterm oxygen statistically different from the rest by ANOVA ( $p < 0.001$ ).

**Table**

Baseline characteristics and carotid arterial blood gases prior to delivery

Parameters (in mean $\pm$ S.D)	Preterm lambs			Term lambs
	100% oxygen (N=6)	Titrated Oxygen (N=16)	21% oxygen (N=7)	21% oxygen (N=7)
Weight (kg)	3.1 $\pm$ 0.4	2.9 $\pm$ 0.6	2.8 $\pm$ 0.4	4.0 $\pm$ 0.6 *
Female n (%)	3 (50%)	7 (44%)	4 (57%)	3 (43%)
Twins n (%)	2 (33%)	5 (31%)	2 (29%)	2 (29%)
pH	7.15 $\pm$ 0.20	7.12 $\pm$ 0.12	7.13 $\pm$ 0.19	7.2 $\pm$ 0.2
PaCO <sub>2</sub> – (mm Hg)	84.9 $\pm$ 27.0	83.7 $\pm$ 26.5	81.3 $\pm$ 24.0	77 $\pm$ 20.5

\*  
p<0.05, data presented as mean & SD unless specified